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FORM PTO-1390 (REV. 1-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		41482/205543 U.S. APPLICATION NO. (If known, see 37 CFR 09/ 980329
INTERNATIONAL APPLICATION NO. PCT/US00/16471	INTERNATIONAL FILING DATE 14 June 2000 (14.06.00)	PRIORITY DATE CLAIMED 14 June 1999 (14.06.99)
TITLE OF INVENTION METHOD AND KIT FOR CAVITATION-INDUCED TISSUE HEALING WITH LOW INTENSITY ULTRASOUND		
APPLICANT(S) FOR DO/EO/US WINDER, Alan A. and TALISH, Roger J.		

Applicants herewith submit to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 37 (b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as published (35 U.S.C. 371(c)(2))
   - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   - b. ☐ has been transmitted by the International Bureau.
   - c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the published International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   - b. ☐ have been transmitted by the International Bureau.
   - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). (unexecuted)
10. ☐ A translation of the annexes of the International Preliminary Examination Report under PCT Article 36
11. ☐ An Information Disclosure Statement under 37 CFR 1.197 and 1.98
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:
    - a. Certification Under 37 CFR 1.10

      I hereby certify that this document is being mailed to Box PCT, Commissioner for Patents, Washington, D.C. 20231, via "Express Mail Post Office to Addressee" on this 30TH day of November, 2001, Express Mail Label No. EL209600078US

      Angela M. Rossi ____ Angela M. Rossi
    - b. Version with markings to show changes made

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U.S. APPLICATION NO. (if known, see 37 CFR 1.5) unknown 09/980329	INTERNATIONAL APPLICATION NO. PCT/US00/16471	ATTORNEY'S DOCKET NUMBER 41482/205543

17. ☒ The following fees are submitted BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):				CALCULATIONS	PTO USE ONLY
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO			$1,040.00		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO			$890.00		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2) paid to USPTO			$740.00		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)			$710.00		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)			$100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT			=	$710.00	
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				$130.00	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	$	
Total claims	24	04	X $18.00	$72.00	
Independent claims	03	00	X $84.00	$.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+$280.00	$.00	
TOTAL OF ABOVE CALCULATIONS			=	$912.00	
Reduction of ½ for filing by small entity, if applicable.			--	$.00	
SUBTOTAL			=	$912.00	
Processing fee of $130.00 for furnishing the English translation later than ☐20 ☐30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$.00	
TOTAL NATIONAL FEE			=	$912.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40 per property				$.00	
TOTAL FEES ENCLOSED			=	$912.00	
				Amount to be refunded:	$
				charged:	$

a. ☒ Check in the amounts of $912.00 is enclosed.

b. ☐ Please charge my Deposit Account No. 11-0855 in the amount of $______ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 11-0855.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Chief Patent Counsel
Smith & Nephew, Inc.
1450 Brooks Road
Memphis, Tennessee 38116

30559
PATENT TRADEMARK OFFICE

SIGNATURE

Name: Bruce D. Gray
Registration No. 35,799

1254817

IN THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

Applicants: Alan A. WINDER and Roger J.TALISH

International Application No.: PCT/US00/16471

U.S. Serial No.:

International Filing Date: 14 June 2000 (14.06.00)

U.S. Filing Date: 30 November 2001 (30.11.01)

For: METHOD AND KIT FOR CAVITATION-INDUCED TISSUE HEALING WITH LOW INTENSITY ULTRASOUND

Box PCT
Commissioner for Patents
Washington, D.C. 20231

Attorney Docket No. 41482/205543
Date: 30 November 2001

PRELIMINARY AMENDMENT

Sir:

Kindly amend the above-identified patent application prior to examination:

In the specification

On page 1, please delete the paragraph following the heading entitled "PRIORITY" and insert the following paragraph in place thereof:

--This application is the U.S. national phase of International Application No. PCT/US00/16471 filed on 14 June 2000 which claims priority to U.S. Provisional Application No. 60/139,124 filed on 14 June 1999 by Alan A. Winder and Rogert J. Talish, the contents of which are incorporated herein by reference.--

In the claims

Please amend the claims as indicated below:

1. (Amended) A method for therapeutically treating an injury using ultrasound, the method comprising the steps of

introducing an ultrasound contrast agent into a patient; and

impinging ultrasonic waves in proximity to the injury, wherein the ultrasound contrast agent facilitates in lowering the cavitation threshold to an intensity level attainable by the ultrasonic waves.

2. (Amended) The method according to Claim 1, further comprising the step of maintaining the acoustic spatial average-temporal average (SATA) intensity of the ultrasonic waves from about 5 to 500 mW/cm^2.

11. (Amended) A kit for therapeutically treating an injury using ultrasound, the kit comprising:

an ultrasonic transducer assembly having at least one ultrasonic transducer;

an ultrasonic signal generator coupled to the ultrasonic transducer assembly;

a main operating unit electrically coupled to the ultrasonic signal generator for transmitting at least one signal thereto activating the at least one ultrasonic transducer; and

an ultrasound contrast agent.

17. (Amended) The kit according to claim 11, wherein the ultrasonic signal generator includes signal generator circuitry and an internal power source connected to the signal generator circuitry.

20. (Amended) A method for therapeutically treating an injury using ultrasound, the method comprising the steps of:

providing a main operating unit having an internal power source coupled to an ultrasonic transducer assembly, the ultrasonic transducer assembly includes at least one ultrasonic transducer, an ultrasonic signal generator and signal generator circuitry therein;

providing a placement module configured for receiving the ultrasonic transducer assembly and for placing the at least one ultrasonic transducer in proximity to the injury;

introducing an ultrasound contrast agent into the patient; and

exciting the at least one ultrasonic transducer to impinge ultrasonic waves at or near the injury, wherein the ultrasound contrast agent facilitates in lowering the cavitation threshold to an intensity level attainable by the ultrasonic waves.

Please add the following claims:

21. (New) The method according to Claim 3, wherein the radii of the microbubbles of the ultrasound contrast agent are less than 7.0 µm.

22. (New) The method according to Claim 10, wherein the step of transmitting a signal to the sensor comprises instructing the capsule to release the ultrasound contrast agent in preset amounts at multiple predetermined time intervals.

23. (New) The method according to Claim 15, wherein the radii of the microbubbles of the ultrasound contrast agent are less than 7.0 µm.

24. (New) The method according to Claim 17, wherein the signal generator circuitry comprises a processor and means for generating a pulsed RF signal.

Respectfully submitted,

Bruce D. Gray
Reg. No. 35,799

KILPATRICK STOCKTON LLP
Suite 2800
1100 Peachtree Street
Atlanta, Georgia 30309-4530
(404) 815.6218

U.S. National Phase of PCT/US00/16471
Filed: 30 November 2001
Preliminary Amendment

Version with markings to show changes made

In the specification

This application is the U.S. national phase of International Application No. PCT/US00/16471 filed on 14 June 2000 which claims priority to a U.S. Provisional Application No. 60/139,124 filed on June 14, 1999 by Alan A. Winder, et al., the contents of which are incorporated herein by reference.

In the claims

1. (Amended) A method for therapeutically treating an injury using ultrasound, the method comprising the steps of

introducing an ultrasound contrast agent into a patient; and

impinging ultrasonic waves in proximity to the injury, wherein the ultrasound contrast agent facilitates in lowering the cavitation threshold to [a] an intensity level attainable by the ultrasonic waves.

2. (Amended) The method according to Claim 1, further comprising the step of maintaining the acoustic spatial average-temporal average (SATA) intensity of the ultrasonic waves from about 5 to 500 mW/cm^2.

11. (Amended) A kit for therapeutically treating an injury using ultrasound, the kit comprising:

an ultrasonic transducer assembly having at least one ultrasonic transducer;

an ultrasonic signal generator [positioned in] coupled to the ultrasonic transducer assembly;

a main operating unit electrically coupled to the ultrasonic signal generator for transmitting at least one signal thereto [for] activating the at least one ultrasonic transducer [for emitting ultrasonic waves]; and

an ultrasound contrast agent.

17. (Amended) The kit according to claim 11, wherein the ultrasonic signal generator includes signal generator circuitry and an internal power source connected to the signal

generator circuitry[, and the signal generator circuitry including a processor and means for generating a pulsed RF signal].

20. (Amended) A method for therapeutically treating an injury using ultrasound, the method comprising the steps of:

providing a main operating unit having an internal power source coupled to an ultrasonic transducer assembly, the ultrasonic transducer assembly includes at least one ultrasonic transducer, an ultrasonic signal generator and signal generator circuitry therein;

providing a placement module configured for receiving the ultrasonic transducer assembly and for placing the at least one ultrasonic transducer in proximity to the injury;

introducing an ultrasound contrast agent into the patient; and

exciting the at least one ultrasonic transducer to impinge ultrasonic waves at or near the injury, wherein the ultrasound contrast agent facilitates in lowering the cavitation threshold to [a] <u>an intensity</u> level attainable by the ultrasonic waves.

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METHOD AND KIT FOR CAVITATION-INDUCED TISSUE HEALING WITH LOW INTENSITY ULTRASOUND

PRIORITY

This application claims priority to a U.S. Provisional Application No. 60/139,124 filed on June 14, 1999 by Winder et al.; the contents of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a method and kit for therapeutically treating injuries by inducing acoustic intracellular microstreaming by using low intensity ultrasound. More particularly, the present invention relates to a method and kit which utilizes an ultrasound contrast agent and an ergonomically constructed ultrasonic transducer for placement in proximity to an injury for therapeutically treating the injury by producing acoustic cavitation at the trauma site. The ultrasound contrast agent is introduced into the patient, preferably, the patient's blood stream, prior to emitting ultrasonic waves toward the trauma site to lower the cavitation threshold, i.e., the energy required for cavitation, to a level attainable with low intensity ultrasound.

2. Description of the Related Art

The use of ultrasound or acoustic energy to therapeutically treat and evaluate bone and tissue injuries is known. Impinging ultrasonic pulses having appropriate parameters, e.g., frequency, pulse repetition, and amplitude, for suitable periods of time and at a proper external location adjacent to a bone or tissue injury has been determined to accelerate the natural healing of, for example, bone breaks and fractures.

U.S. Patent No. 4,530,360 to Duarte describes a basic non-invasive therapeutic technique and apparatus for applying ultrasonic pulses from an operative surface placed on the skin at a location adjacent a bone injury. The applicator

described in the Duarte patent has a plastic tube which serves a grip for the operator, an RF plug attached to the plastic tube for connection to an RF source, and internal cabling connected to an ultrasonic transducer. To apply the ultrasound pulses during treatment an operator must manually hold the applicator in place until the treatment is complete. As a result, the patient is, in effect, immobilized during treatment. The longer the treatment period, the more the patient is inconvenienced. The Duarte patent as well as U.S. Patent No. 5,520,612 to Winder et al. describe ranges of RF signal for creating the ultrasound, ultrasound power density levels, ranges of duration for each ultrasonic pulse, and ranges of ultrasonic pulse frequencies.

U.S. Patent No. 5,003,965 to Talish et al. relates to an ultrasonic body treatment system having a body-applicator unit connected to a remote control unit by sheathed fiber optic lines. The signal controlling the duration of ultrasonic pulses and the pulse repetition frequency are generated apart from the body-applicator unit. Talish et al. also describes a mounting fixture for attaching the body-applicator unit to a patient so that the operative surface is adjacent the skin location.

It has been demonstrated that the components of acoustic energy that can effect chemical change can be thermal, mechanical (agitational) and cavitational in nature. The largest non-thermal effects are those attributed to stable cavitation and mass transfer. These, in turn, can induce acoustic microstreaming, producing shear stresses on the cellular wall and boundary layer, and in the cytosol. The latter effect, due to intracellular microstreaming, can produce an increase in the metabolic function of the cell.

Since the early sixties, the specific physical and biological mechanisms behind the therapeutic effectiveness of low intensity ultrasound have been extensively investigated. For spatial average-temporal average (SATA) intensities from 0.1 - 0.5 W/cm^2, it is possible to produce the non-thermal, high stress mechanisms of acoustic streaming and cavitation. In vitro tests on isolated fibroblast cells have shown that the effects of ultrasound on the cells are pressure sensitive, suggesting a (stable) cavitation mechanism, caused by the rapid expansion and collapse of microbubbles. The resulting bubble oscillations, possibly including acoustic microstreaming, can

generate high shear stress on the cell membrane, which can affect the cell's permeability to sodium and calcium ions. The increase in cell permeability may result in an increase in calcium uptake, an increase in protein and DNA synthesis in fibroblasts, and account for the observed activation of macrophages. The production of fibroblasts and macrophages characterizes the normal fracture repair process.

It has been determined that the cavitation threshold, i.e., the energy required for cavitation, is approximately 0.1 W/cm^2 in an aqueous medium and approximately 0.2 W/cm^2 in vivo. One in vivo study conducted utilizing a simulated cell membrane attributed the measured ultrasound-induced changes in the properties of cell membranes to changes in diffusion rates produced by fluid layer movement near the membrane. It has also been demonstrated that the value of micromechanical stimuli (0.5 Hz for 17 minutes, daily) significantly improves the healing of tibial fractures. One study was able to correlate this accelerated healing process with the promotion of fracture revascularization. However, for SATA intensities below 0.1 W/cm^2, stable cavitation and acoustic micro-streaming seem quite unlikely. In another study, exposure to low intensity ultrasound produced increased levels of aggrecan mRNA in a rat femur model in the early stages of treatment.

In vivo test results indicate that a low SATA intensity from 30-50 mW/cm^2 is highly effective in stimulating bone fracture repair. These results support the thesis that ultrasonically-induced mechanical vibrations tend to increase the permeability of the cell membrane.

In other clinical studies, preliminary results indicate that angiogenesis, the development of new blood vessels, is a key component in the initial phase in the cascade of events involved in the bone fracture healing process. The increased vascularity and the micromechanical fluid pressure appear to produce an increase in cellular calcium uptake, resulting in increased protein synthesis, thereby accelerating bone fracture healing and tissue repair.

Accordingly, there is a need for a method and kit for accelerating bone and tissue healing utilizing the scientific and anatomical observations and studies discussed above. That is, there is a need for a method and kit for accelerating bone

and tissue healing by lowering the cavitation threshold to a level attainable with low intensity ultrasound to produce acoustic intracellular microstreaming. Since intracellular microstreaming can produce an increase in the metabolic functions, the method and kit would accelerate the healing process.

SUMMARY OF THE INVENTION

The method and kit of the present invention is used for therapeutically treating bone and tissue injuries using low intensity ultrasound. The method includes the steps of introducing an ultrasound contrast agent into the patient, preferably, the patient's blood stream, and impinging ultrasonic waves in proximity to an injury, wherein the ultrasound contrast agent facilitates in lowering the cavitation threshold, i.e., the energy required for cavitation, to a level attainable by the low intensity ultrasonic waves. It is preferred that the ultrasonic waves exhibit an intensity from about 0.1 to 0.5 W/cm^2 to produce non-thermal, high-stress mechanisms of acoustic intracellular microstreaming and cavitation.

The present invention also provides a kit for therapeutically treating bone and tissue injuries using low intensity ultrasound. The kit includes an ultrasonic transducer assembly having at least an ultrasonic transducer, a placement module configured to be worn by a patient and to receive the ultrasonic transducer assembly, an integrated ultrasonic signal generator located in the ultrasonic transducer assembly, a main operating unit (MOU) or controller, a pouch constructed to receive the MOU, and an ultrasound contrast agent provided in a syringe or a capsule in sufficient quantity for the treatment time.

Preferably, the MOU has an internal power source for powering the signal generator circuitry, a display coupled to the signal generator circuitry to display treatment sequence data, and a keypad coupled to the signal generator circuitry to permit user operation and/or entry of data. Further, the MOU is fitted within the pouch which is reliably secured to a patient during treatment, thereby providing patient mobility. Timing control circuitry, as well as monitoring circuitry for the proper attachment and operation of the ultrasonic transducer assembly, are also

housed within the MOU. A MOU envisioned for use with the present invention is described in U.S. Patent No. 5,556,372 to Talish et al.; the contents of which are hereby incorporated by reference.

The signal generator circuitry includes a processor, means for generating a pulsed control signal, and a switch coupled to the processor for regulating the pulsed control signal. A communication interface may be connected between a communication port and the processor to provide a communication link between the ultrasonic signal generator and an external computer or modem. Preferably, the communication interface is a serial communication interface, however, a parallel interface is also contemplated. An alarm may be provided to indicate to the user that the treatment time has expired. The alarm is coupled to the processor such that when ultrasonic treatment is completed the processor activates the alarm and terminates ultrasound generation.

In operation, the MOU is electrically coupled to the at least one transducer of the ultrasonic transducer assembly for transmitting signals to the at least one transducer for controlling the same. The ultrasound contrast agent is preferably introduced into the blood stream to induce acoustic intracellular microstreaming to lower the cavitation threshold to a level attainable with the ultrasonic waves to be emitted by the at least one transducer. The at least one transducer is then excited to impinge ultrasonic waves for a predetermined period of time against the trauma site.

It is contemplated that the ultrasonic waves may be emitted away from the trauma site and reflected toward the trauma site by a bone or an implanted inorganic material, such as a metallic plate. It has been demonstrated that the acoustic intracellular microstreaming produces an increase in the metabolic functions of the cell, thereby accelerating the healing process.

BRIEF DESCRIPTION OF THE DRAWINGS

Preferred embodiments of the invention are described below with reference to the drawings, which are described as follows:

Fig. 1 is a perspective view with parts separated of a portable ultrasonic treatment kit according to the present invention, illustrating a main operating unit or controller, a placement module, an ultrasound contrast agent housed within a syringe, and an ultrasound contrast agent encapsulated in a delivery/release system;

Fig. 2 is a perspective view of a patient wearing the portable treatment apparatus of Fig. 1;

Fig. 3 is a cross-sectional view along line 3-3 in Fig. 2 illustrating the transducer assembly impinging ultrasonic waves after the ultrasound contrast agent has been introduced into the patient;

Fig. 4A is a block diagram of one embodiment of the circuitry for the ultrasonic transducer assembly; and

Fig. 4B is a block diagram of an alternative embodiment of the circuitry for the ultrasonic transducer assembly.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The ultrasonic treatment method and kit of the present invention is used for the surgically non-invasive utilization of low intensity acoustic energy to accelerate the healing process for treating bone and tissue injuries. The present invention uses the concept that the bone fracture and wound healing process can be further enhanced and accelerated if the mechanisms of stable cavitation and microstreaming are induced within the low intensity ultrasound regime. This will have several important biological effects: (1) it will further increase the permeability of the cellular wall membrane, enhancing the diffusion process for calcium uptake and protein synthesis, (2) increase the amount of hemoglobin released, (3) effect the gene expression within the insonated tissue, and (4) assist in the removal of debris from the trauma site.

At the frequencies generally employed for therapeutic and diagnostic ultrasound, from 0.1 MHz to 10 MHz, the cavitation threshold, i.e., the energy required for cavitation, occurs at pressure levels exceeding 5 MPa. However,

ultrasound contrast agents having gas-filled microbubbles, with radii preferably from 0.4 to 1.0 μm, have been observed to lower the cavitation threshold to less than 0.2 MPa, a factor of more than twenty-five, when targeted or impinged with acoustic energy.

Ultrasound contrast agents are nontoxic, are usually injected intravenously, can pass through the pulmonary, cardiac and capillary circulation systems, increase the backscatter only with high tissue contrast, and recirculate through the systems during a medical examination. Most of the agents consist of gas-filled microbubbles with bubble resonance frequencies in the 0.5 to 10 MHz range which is the frequency range for most therapeutic and diagnostic ultrasound medical applications. Fortunately, these correspond to bubble sizes less than 7.0 microns, small enough to pass through pulmonary, cardiac and capillary circulations. The backscattered energy can be increased by either increasing the contrast concentrations or by causing free air bubbles to resonate within the fluid, producing scattering cross-sections several orders of magnitude larger than their geometric cross-sections.

Clinically, it has been demonstrated that ultrasound contrast agents can significantly enhance the detection of blood flow in small malignant breast tumors, in small deep vessels in the abdomen, help differentiate tumor and normal tissue vascularity, aid in the detection of ischemia or occlusion and improve the visualization of vascular stenosis. Examples of ultrasound contrast agents are Definity™ (Dupont Pharmaceuticals, Bellerica, Massachusetts), Sonazoid™ (Nycomed-Amersham, Oslo, Norway), Optison™ (Molecular Biosystems, Inc., San Diego, California), Imagent™ (Alliance Pharmaceutical Corp., San Diego, California), and SonoRx™ (Bracco Diagnostics, Princeton, New Jersey).

The pressure level at which the cavitation threshold is lowered, by the use of ultrasound contrast agents having gas-filled microbubbles with radii from 0.4 to 1.0 μm, is almost equal to that defined by the spatial peak temporal average (SPTA) acoustic intensity for the Sonic Accelerated Fracture Healing (SAFHS™) ultrasonic transducer manufactured by Exogen, Inc. of Piscataway, New Jersey. From 1995 to 1999, a set of twenty-one measurements were made of SAFHS™

transducers at a frequency of 1.5 MHz by Sonic Technologies, located in Hatboro, Pennsylvania, resulting in a sample mean (far-field) SPTA of 110.34 mW/cm^2, with an unbiased sample standard deviation of 4.02 mW/cm^2.

In any given plane in the acoustic field, the SPTA acoustic intensity, I, can be expressed as:

$$I = [\text{Integral of Waveform Squared}] \bullet \text{PRF}/K_f^2 \ \ \text{W/cm}^2,$$

where the term in the brackets is essentially the energy in the waveform, PRF is the pulse repetition frequency and K_f^2 is often referred to in the literature as the intensity response factor. If the transmitted signal is a pulsed sine wave of rectangular envelope, given by $V(t) = V_o \sin 2\pi f_c t$, with pulse length 2T and carrier frequency f_c, then

$$I = P_o{}^2 T\,(\text{PRF})/(10^4\,\rho c) \ \ \text{W/cm}^2,$$

where P_o is the peak pressure in Pascal. The relevant parameters for soft tissue and the SAFHS® transducer are: ρ=1000 kg/m^3, c=1496 m/s, PRF=1.0 kHz, T=100 µsecs and f_c=1.50 MHz, resulting in the following relationship between the peak pressure (in MPa) and SPTA intensity (in mW/cm^2) in tissue:

$$P_o = \{0.00015 \times I\}^{1/2} \ \text{MPa}.$$

For a duty cycle of 20%, a SATA intensity of 30 mW/cm^2 results in a SPTA intensity of approximately 97.2 mW/cm^2, which in turn, results in a peak pressure of 0.12 MPa. Therefore, by introducing microbubbles into the system, a SATA intensity from 80 to 100 mW/cm^2 can produce peak pressure levels that exceed the cavitation threshold.

In line with the above mathematical relationships, the principles of the present invention entail administering an ultrasound contrast agent having gas-filled microbubbles to a patient and subsequently inducing acoustic intracellular microstreaming by transmitting acoustic energy using an ultrasonic transducer. Accordingly, the kit of the present invention includes an ergonomically constructed placement module having a strap or other fastening means for being secured to an injured part of a patient's body. At least one ultrasonic transducer assembly partially

fabricated with a conductive plastic material is attached or imbedded within the placement module and properly positioned in proximity to the trauma site.

Different types of ultrasonic transducers and signals can be provided, such as those described and schematically depicted in U.S. Patent No. 5,520,612 to Winder et al.; the contents of which are hereby incorporated by reference. Particularly, the transducers and arrangements schematically depicted by Figs. 7-11 of the patent in which at least one transducer is used to provide acoustic energy to the site of the injury. The kit also utilizes a portable, ergonomically constructed main operating unit (MOU) which is constructed to fit within a pouch worn by the patient using belt and shoulder strap and provides control signals to the ultrasonic transducers. The MOU which is utilized is preferably the one described in U.S. Patent No. 5,556,372 to Talish et al.; the contents of which are hereby incorporated by reference.

Turning to the figures, in particular Fig. 1, a preferred embodiment of the portable ultrasonic treatment kit 10 of the present invention is shown. The ultrasonic treatment kit 10 includes a MOU 12, a placement module 14, an ultrasonic transducer assembly 16, a pouch 18 for reliably securing the MOU 12 to the patient during treatment for providing patient mobility, and a syringe 100 housing an ultrasound contrast agent 102 having gas-filled microbubbles. The syringe 100 is used for intravenously introducing the contrast agent 102 into the patient's body, preferably, the patient's blood stream, prior to administering ultrasonic treatment as further described below. The kit 10 further includes a delivery/release system 106 as further described below.

It is contemplated that the microbubbles can be swallowed in capsule form. The capsule can be designed to be timed-release, and the microbubbles released internally at a controlled, designated time. The required capsule, timed-release technology is well known to the pharmaceutical industry (e.g., Andryx Corporation, Fort Lauderdale, Florida, manufactures such timed-release capsules).

The placement module 14 is comprised of placement bands 20 and placement support 22. The placement support 22 includes a pocket 24 adapted for

placement of the ultrasonic transducer assembly 16 therein. The placement support 22 further includes a body rest 26 having slots 30 for connecting the placement support 22 to the placement bands 20. A sponge-like material 34 lines the inner surface of the placement support 22 for providing comfort to the patient. The placement support 22 may be construed of hard plastics which may be custom molded for a particular patient.

The transducer assembly 16 includes circuitry, schematically illustrated by Figs. 4A and 4B and described below, for exciting at least one transducer therein and is coupled to the MOU by cable 36. The cable 36 is preferably a multiconductor cable capable of transmitting relatively low frequency RF or optical signals, as well as digital signals. The cable 36 may include coaxial cable or other types of suitable shielded cable. Alternatively, the cable 36 may include fiber optic cable for transmitting optical signals. The signals may be transmitted continuously or as a series of pulses.

In operation, the placement module 14 is positioned and secured to the patient's body as shown by Fig. 2, such that the transducer assembly 16 lies over or in proximity to an injury. A locating ring such as the one disclosed in U.S. Patent Application No. 08/389,148 may be used for determining the location of injured bone in the case of a bone injury before the placement module 14 is secured to the patient. Once the placement module 14 is properly positioned (or prior to being properly positioned), the ultrasound contrast agent 102 having the gas-filled microbubbles is introduced into the patient's body intravenously using the syringe 100 (indicated by step I in Fig. 2). The microbubbles are designed to stay in the system over a period of time from as little as one to at least twenty minutes. The microbubbles act as cavitation nuclei to increase cell membrane permeability and to enhance the angiogenesis process that is part of the cascade of biological events in the tissue healing process.

The transducer within the transducer assembly 16 is then excited for a pre-determined amount of time (indicated by step II in Fig. 2). A gel-like substance 38 is positioned between the transducer assembly 16 and the injured part of the

patient's body to increase the acoustic coupling of the ultrasonic waves emitted from the transducer to the outer skin-soft tissue of the body, as shown by Fig. 3. With the presence of ultrasonic waves, the microbubbles become acoustically active targets with ultrasound insonification, thereby causing cavitation to occur at low pressure levels to accelerate the healing process.

The kit 10 of the present invention permits the bubble resonance frequency, the bubble radii, the SATA intensity and the transmitting frequency of the ultrasonic waves to be controllable to significantly lower the cavitation threshold to levels produced by low intensity ultrasound. For example, the transmit frequency of the ultrasonic waves can be controlled to range from 10 kHz to 10 MHZ, the bubble radii from 0.1 to 10.0 μm, and SATA intensities from about 5 to 500 mW/cm^2. It is contemplated that the optimum values for these parameters for a particular patient are predetermined and set accordingly during treatment to achieve optimum healing.

With reference to Fig. 1 and as indicated above, the kit 10 further includes another ultrasound contrast agent 104 in a delivery/release system 106 that facilitates the "targeting" of the agent(s) 104 to a specific location in the body. Delivery/release systems are known in the art. The system 106 has the advantage of delivering the agent(s) 104 precisely to the trauma site for cellular metabolic action to occur.

In its simplest form, the capsule 108 exists without a sensor and associated circuitry, and is configured as a chemically-controlled timed-release system, with contrast agent(s) 104. In a more complex configuration, the delivery/release system 106 is contemplated to have the capsule 108 containing a non-lead piezoelectric sensor 110, such as polyvinylidene fluoride (PVDF), for receiving and responding to an acoustic signal, and a compartment 112 for the contrast agent(s) 104.

During operation, the ultrasonic transducer assembly 16 is applied to the skin of the body at or near the site of the bone fracture or tissue wound and activated to administer the normal therapeutic dosage. The transmitted acoustic signal is detected by the sensor 110 in the capsule 108, thereby releasing a

predetermined amount of the contrast agent(s) 104 within the compartment 112 of the capsule 108. It is contemplated that the capsule 108 includes a processor which is programmed by chemical and/or electromagnetic means for releasing the agent(s) 104 at different locations of the body, in preset amounts, at multiple, predetermined time intervals. After total agent release, the remaining part of the capsule 108 is discarded naturally as a waste product.

With reference to Fig. 4A, a block diagram of one embodiment of the ultrasonic transducer assembly circuitry is shown. The transducer assembly circuitry 17 includes an RF oscillator 50 which receives the signals transferred by a signal generator within MOU 12 via cable 36. RF oscillator 50 is connected to transducer driver 52 which excites transducer 54.

An alternative embodiment of the transducer assembly circuitry 17 is shown in Fig. 4B. In this embodiment, the ultrasonic transducer assembly 16 includes an internal battery 60 which supplies power to the components within the transducer assembly 16. For example, battery 60 supplies power to signal monitoring circuit 62 and signal driver 66. The signal monitoring circuit 62 provides, preferably, a digital output signal 68 which represents the waveform characteristics of the output of transducer driver 70. These characteristics can be displayed on a digital display and may include, for example, the frequency, pulse repetition frequency, the pulse width and the average output power of the transducer 54. The output signal 68 of signal monitoring circuit 62 is transferred to the signal generator within MOU 12 via driver 66 and cable 36. The signal generator may include a processor and a switch for regulating the signal characteristics. Control signals from the MOU 12 are received by receiver 72 via cable 36. Safety or fixture interlock 74, which may include switches on the outer surface of the placement module 14 or transducer assembly 16, ensures that the placement module 14 is properly positioned before providing power to the internal components of the transducer assembly 16. That is, fixture interlock 74 prevents inadvertent activation of the transducer assembly 16.

It will be understood that various modifications can be made to the various embodiments of the present invention herein disclosed without departing

from its spirit and scope. For example, various methods of introducing the ultrasound contrast agent(s) into the patient's body are foreseen other than intravenously or in capsule form. Also, various modifications may be made in the structural configuration of the placement module and the configuration of the components used to excite the ultrasonic transducer. Therefore, the above description should not be construed as limiting the invention but merely as presenting preferred embodiments of the invention. Those skilled in the art will envision other modifications within the scope and spirit of the present invention as defined by the claims presented below.

WHAT IS CLAIMED IS:

1. A method for therapeutically treating an injury using ultrasound, the method comprising the steps of:

introducing an ultrasound contrast agent into a patient; and

impinging ultrasonic waves in proximity to the injury, wherein the ultrasound contrast agent facilitates in lowering the cavitation threshold to a level attainable by the ultrasonic waves.

2. The method according to Claim 1, further comprising the step of maintaining the acoustic spatial average-temporal average (SATA) intensity of the ultrasonic waves from 5 to 500 mW/cm^2.

3. The method according to Claim 1, wherein the ultrasound contrast agent is comprised of microbubbles having a radius from 0.1 to 10.0 μm.

4. The method according to Claim 3, further comprising the step of maintaining the resonance bubble frequency of the microbubbles from 0.5 MHz to 10 MHz.

5. The method according to Claim 1, further comprising the step of maintaining the acoustic transmit frequency of the ultrasonic waves from 10 kHz to 10 MHz.

6. The method according to Claim 1, further comprising the step of terminating the impinging step after approximately thirty minutes.

7. The method according to Claim 1, wherein the step of introducing comprises the step of time-releasing the ultrasound contrast agent into the patient.

8. The method according to Claim 1, wherein the step of introducing comprises the step of using a syringe to intravenously introduce the ultrasound contrast agent into the patient.

9. The method according to Claim 1, wherein the step of introducing comprises the steps of:

placing the ultrasound contrast agent within a timed-release capsule; and

placing the timed-released capsule within the patient.

10. The method according to Claim 1, wherein the step of introducing comprises the steps of:

placing a capsule housing a sensor and the ultrasound contrast agent inside the patient; and

transmitting a signal to the sensor instructing the capsule to release the ultrasound contrast agent.

11. A kit for therapeutically treating an injury using ultrasound, the kit comprising:

an ultrasonic transducer assembly having at least one ultrasonic transducer;

an ultrasonic signal generator positioned in the ultrasonic transducer assembly;

a main operating unit electrically coupled to the ultrasonic signal generator for transmitting at least one signal thereto for activating the at least one ultrasonic transducer for emitting ultrasonic waves; and

an ultrasound contrast agent.

12. The kit according to Claim 11, wherein the ultrasound contrast agent is housed within a syringe.

13. The kit according to Claim 11, wherein the ultrasound contrast agent is housed within a timed-release capsule.

14. The kit according to Claim 11, wherein the ultrasound contrast agent is housed within a delivery/release system having means for responding to the ultrasonic waves.

15. The kit according to Claim 11, wherein the ultrasound contrast agent is comprised of microbubbles having radii from 0.1 to 10.0 μm.

16. The kit according to Claim 11, further comprising a placement module configured to be worn by a patient, the placement module being configured to receive the transducer assembly such that when the placement module is worn the at least one ultrasonic transducer is positioned in proximity to the injury.

17. The kit according to claim 11, wherein the ultrasonic signal generator includes signal generator circuitry and an internal power source connected to the signal generator circuitry, and the signal generator circuitry including a processor and means for generating a pulsed RF signal.

18. The kit according to claim 11, wherein the main operating unit is positioned within a pouch worn by the patient to permit portable operation thereof.

19. The kit according to claim 11, further comprising a gel-like substance for acoustically coupling the ultrasonic waves, emitted by the at least one ultrasonic transducer, to the body of the patient.

20. A method for therapeutically treating an injury using ultrasound, the method comprising the steps of:

providing a main operating unit having an internal power source coupled to an ultrasonic transducer assembly, the ultrasonic transducer assembly includes at least one ultrasonic transducer, an ultrasonic signal generator and signal generator circuitry therein;

providing a placement module configured for receiving the ultrasonic transducer assembly and for placing the at least one ultrasonic transducer in proximity to the injury;

introducing an ultrasound contrast agent into the patient; and

exciting the at least one ultrasonic transducer to impinge ultrasonic waves at or near the injury, wherein the ultrasound contrast agent facilitates in lowering the cavitation threshold to a level attainable by the ultrasonic waves.

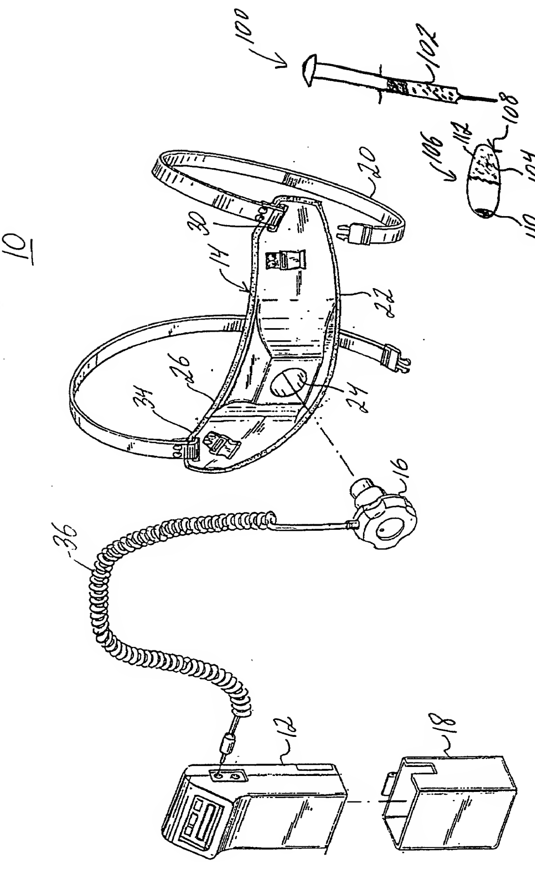

FIG. 1

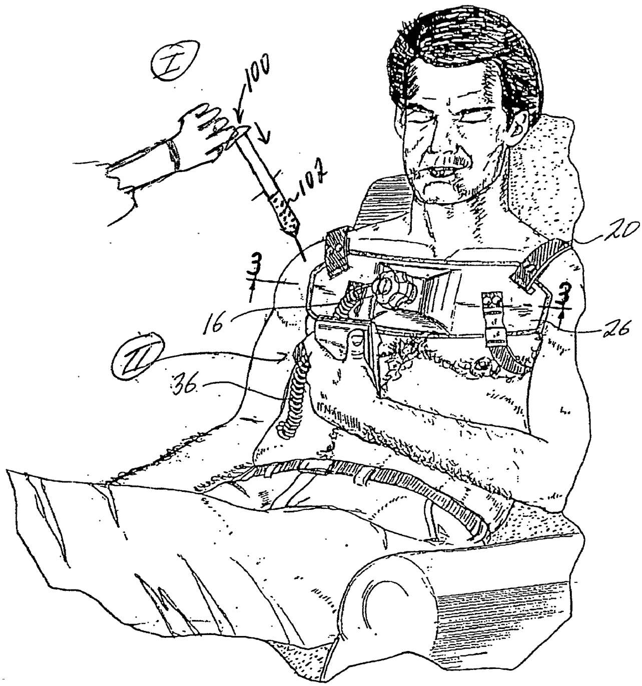

FIG. 2

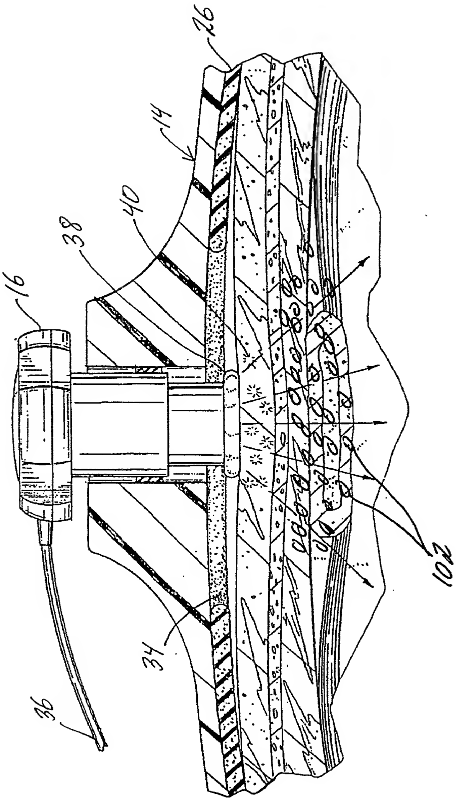

FIG.3

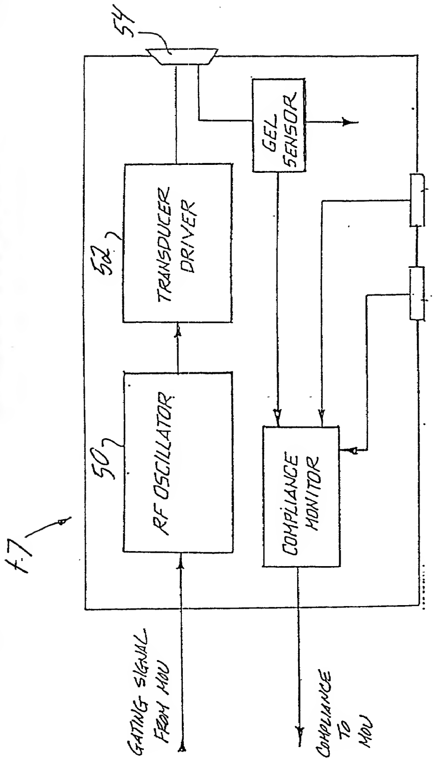
54
GEL SENSOR
52
TRANSDUCER DRIVER
50
RF OSCILLATOR
COMPLIANCE MONITOR
47
GATING SIGNAL FROM MOU
COMPLIANCE TO MOU

FIG. 4A

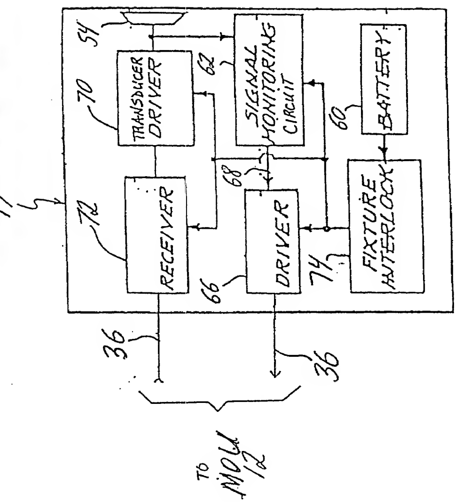
TRANSDUCER DRIVER
SIGNAL MONITORING CIRCUIT
BATTERY
RECEIVER
DRIVER
FIXTURE INTERLOCK
54
70
62
60
17
72
68
66
74
36
36
TO MOU 12

FIG. 4B

Attorney Docket No. 41482/205543
Express Mail Label No. EL209600078US

DECLARATION FOR PATENT APPLICATION

☒ Original ☐ Supplemental ☐ Substitute ☐ PCT

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below), or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

METHOD AND KIT FOR CAVITATION-INDUCED TISSUE HEALING WITH LOW INTENSITY ULTRASOUND
(Title of the Invention)

the specification of which (check one)

☐ is attached hereto

☒ was filed on 14 June 2000 as International Application Number PCT/US00/16471

and was amended ______________________
(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 (a) - (d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified, by checking the box below, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Applications			Priority Claimed		Copy Attached	
Application Number	Country	Foreign Filing Date (MM/DD/YYYY)	YES	NO	YES	NO

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below and claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT international application(s) designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application(s) in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Parent Application Number	Filing Date	Status (Mark Appropriate Column Below)		
		Patented	Pending	Abandoned
60/139,124	06/14/99			x

As a named inventor, I hereby revoke all prior powers and appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

30559
PATENT TRADEMARK OFFICE

FIRM NAME: **KILPATRICK STOCKTON LLP**, 1100 Peachtree Street, Suite 2800, Atlanta, Georgia 30309-4530

Attorney and/or Agent	Registration No.
Roger T. Frost	22,176
Charles Y. Lackey	22,707
Anthony B. Askew	24,154
John M. Harrington	25,592
Donald R. Andersen	28,280
Robert E. Richards	29,105
John S. Pratt	29,476
A. Jose Cortina	29,733
James L. Ewing, IV	30,630
Stephen M. Schaetzel	31,418
James Dean Johnson	31,771
Charles W. Calkins	31,814
Larry A. Roberts	31,871
Jamie L. Greene	32,467
George T. Marcou	33,014
Dean W. Russell	33,452
Richard T. Peterson	35,320
Charles T. Simmons	35,359
Tracy W. Druce	35,493
Eleanor M. Musick	35,623
Nora M. Tocups	35,717
Bruce D. Gray	35,799
Theodore R. Harper	35,890
Geoff L. Sutcliffe	36,348
Pat Winston Kennedy	36,970
David P. Lecroy	37,869
Suzanne Seavello Shope	37,933
Mitchell G. Stockwell	39,389
Jeffery B. Arnold	39,540

Attorney and/or Agent	Registration No.
J. Steven Gardner	41,772
Theodore M. Green	41,801
Joni Stutman	42,173
Heather D. Carmichael	42,389
Thomas A. Corrado	42,439
John K. McDonald	42,860
Sima Singadia Kulkarni	43,732
Camilla Camp Williams	43,992
Christopher J. Chan	44,070
Li K. Wang	44,393
John William Ball, Jr.	44,433
Dawn-Marie Bey	44,442
Tiep H. Nguyen	44,465
John M. Briski	44,562
Michael J. Dimino	44,657
Kristin L. Johnson	44,807
Paul E. Knowlton	44,842
J. Jason Link	44,874
Cheryl L. Huseman	45,392
Shelby B. Grier	45,785
Jennifer R. Seng	45,851
Vaibhav P. Kadaba	45,865
Greg Moldafsky	46,514
J. Michael Boggs	46,563
Michael K. Dixon	46,665
Tywanda L. Harris	46,758
Kristin D. Mallatt	46,895
Cynthia B. Rothschild	47,040
John C. Alemanni	47,384

Attorney and/or Agent	Registration No.
Houri Khalilian	39,546
Suil Kang	39,723
Mary Anthony Merchant	39,771
Brenda Ozaki Holmes	40,339
Lisa J. Moyles	40,737
Michael J. Turton	40,852
Yoncha L. Kundupoglu	41,130
Scott Zimmerman	41,390
Alana G. Kriegsman	41,747

Attorney and/or Agent	Registration No.
Geoffrey K. Gavin	47,591
Janina Malone	47,768
Aleta A. Mills	47,794
Robert M. Stevens	47,972
Christopher L. Bernard	48,234
Laura M. Kelley	48,441
Michael A. Bush	48,893
Jeffrey S. Bernard	P50,020
Ralph E. Gaskins	P50,136

I acknowledge the above-listed attorneys and agents and their firm Kilpatrick Stockton LLP represent my employer (if I am an employee and this application has been or will be assigned to my employer) or the entity with which I have contracted (if I am an independent contractor and this application has been or will be assigned to such entity) and in such cases do not represent me individually. I further acknowledge I have not established, nor will I seek to establish, any personal attorney/client relationship with Kilpatrick Stockton LLP in connection with this application and understand that, should I require legal representation, I will obtain such, at my expense, other than through Kilpatrick Stockton LLP.

As a named inventor, I hereby also appoint the following attorney(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

Joel Petrow	30,886
William B. Clemmons, Jr.	32,558
George Stacey	35,688
Paul A. Revis	45,040

Send Correspondence to: Chief Patent Counsel
Smith & Nephew, Inc.
1450 Brooks Road
Memphis, Tennessee 38116

30559
PATENT TRADEMARK OFFICE

Direct telephone calls to: Paul A. Revis (901) 399.6960

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor Alan A. WINDER
Inventor's signature Alan A. Winder Date 12/12/01
Residence 56 Patrick Road, ~~Westport,~~ CT Connecticut 06880
Citizenship U.S.
Post Office Address Same

Full name of second inventor Roger J. Talish

Inventor's signature NJ Date 12/12/01

Residence 5 Harman Court, Hillsborough, New Jersey 08876

Citizenship U.S.

Post Office Address Same as above

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